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| EXAMINER | |
|---|---|
| BERTOGLIO, VALARIE E | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 04/25/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/605,415 | MACRAE ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/04;1/07;9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's election with traverse of Group I, claims 1-5,8-24,27-37,40-45,47-50,52-55,57,58 and 60 drawn to a method for evaluating a test agent for the ability to modulate a parameter of heart function using a wild-type zebrafish in the reply filed on 01/10/2007 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to examine Groups I and II together. This is not found persuasive because a search of the transgenic art is necessary for Group II, which is not necessary for Group I. Furthermore, the products used in Groups I and II are different and technical consideration differ as well. It is noted that search burden is not the only factor considered in a restriction practice. Groups I and II are clearly, patentably distinct and non-obvious, one over the other.

In a telephone interview with Ramon Tabtiang on 04/11/2007, it was agreed that claims 13 and 29 were inadvertently grouped with Group I. Claims 13 and 29 are clearly drawn to methods of using a transgenic fish, not a wildtype fish. It was agreed that claims 13 and 29 should be regrouped as part of Group II. In general, Mr. Tabtiang traversed the restriction requirement and the Examiner conceded that, while the traversal of record has been addressed and the restriction requirement is maintained, the requirement will not be made final in light of the instant changes.

Claims 6,7,13,25,26,29;38-39,46,51,56,59 and 61-70 are withdrawn as being drawn to a non-elected invention. The requirement is still deemed proper, however, remains non-final. Claims 1-5,8-12,14-24,27,28,30-37,40-45,47-50,52-55,57,58 and 60 are under consideration in the instant office action.

### *Claim Rejections - 35 USC § 112-2nd paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 32,36 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is unclear because it recites that the method of claim 1 further comprises permeabilizing the zebrafish. However, it is not clear where the permeabilization step takes place within the method or how it relates to the method of evaluating the test agent.

Claim 32 is unclear because it recites that the method of claim 20 further comprises permeabilizing the zebrafish. However, it is not clear where the permeabilization step takes place within the method or how it relates to the method of evaluating the test agent.

Claim 36 is unclear because it is not known to what the average pixel intensity or density is referring. It appears that claim 36 or parent claim 20 may be lacking steps.

Claim 49 is unclear because it is not known to what the average pixel intensity or density is referring. It appears that claim 49 or parent claim 40 may be lacking steps.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1) Claims 1-3,9-12,14-21,23,27-28,30-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Zon (**US2005/0155087**; EFD 12/17/2001) as evidenced by Serbedzija (**US 6,656,449**).

Claim 1 is directed to a method of evaluating a test agent for the ability to modulate a parameter of heart function wherein the method steps comprise contacting a zebrafish heart with a test agent, evaluating a parameter of heart function, and correlating the effect of the agent on the zebrafish to the predicted effect on the heart of a mammal. Claim 2 requires detection of cardiotoxicity. Claim 3 limits that parameter to heart rate. Claim 9 requires that the agent be administered in the culture media while claim 10 requires injection of the agent. Claim 11 requires that the zebrafish be a larva. Claim 14 requires that the method be carried out in an array format. Claim 15 required contacting the fish with a dye. Claim 16 requires a step of permeabilizing the zebrafish. Claims 12 and 17 require use of a second agent to be evaluated. Claim 18 requires that the test agent be a small molecule and claim 19 requires the agent be a protein or nucleic acid. Claims 20-23 and 27,28,30-35 are similar to the above claims, however, they are limited to the parameter being heart contractility. Claim 40,43-45,47 and 48 are similar to those above but are directed to use of a plurality of compounds rather than an individual compound. Claim 45 limits the plurality of compound to that containing a hormone. Claims 52-55,57 and 60 are drawn to a similar screening method, requiring use of an array format.

Zon teaches use of zebrafish to screen the DIVERSet E library (paragraph 0161), for agents that affect cardiac function in zebrafish embryos and larvae (paragraph 0050 and 0060) using a 48 well array format (paragraph 0161). Zon teaches administering the agent in the culture media (paragraph [0012]) or by injection (paragraph [0014]). Parameters to be evaluated included heart rate (paragraph [0060] and wall motion (contractility), which are measured in vivo in the intact fish. Zon teaches correlating effects found in zebrafish to predicted effects on other mammals in teaching that compound have capacity to

improve cardiac function have potential for treating cardiac failure in adults (humans). Zon teaches that the test compound can be a small molecule or a nucleic acid (paragraph 0067) or a hormone and that combinatorial libraries of compounds can be used (paragraph 0067-0068). Zon also taught that larval stages can be used in the method (paragraph 0010). Zon teaches screening multiple compounds in parallel using a multi-well plate. Zon taught administering the agent in a DMSO solution (paragraph 0071), which permeabilizes the zebrafish (see Serbedzija, US 6,656,449 at col. 20, lines 53-58). Zon taught administering a dye (paragraph [0071]) and detecting toxicity of the compound (paragraph [0070] and [0166]).

2) Claims 1-3,5,9-12,14-21,23-24,27-28,30-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Serbedzija (US 6,656,449, filed 09/23/2000).

Serbedzija taught a method of evaluating a test agent comprising method steps of contacting a zebrafish with a test agent, wherein the heart includes cells with a calcium-responsive molecule, and evaluating a parameter of heart function (claim 1). Serbedzija taught screening compounds from the NCI Open Synthetic Compound Collection library (col. 23, lines 7-14) by administering the compounds in 6-96 well assay array plates to wildtype zebrafish embryos (col. 23, lines 35-40). Parameters to be evaluated included heart rate (col. 23, lines 54-55). Serbedzija teaches that the test compound can be a small molecule, nucleic acid or a protein (col. 14, lines 19-43) and that combinatorial libraries of compounds can be used. Serbedzija teaches screening multiple compounds in parallel using a multi-well plate. Serbedizija also taught that larval stages can be used in the method (col. 12, lines 46-47). Serbedzija also teaches permeabilizing the zebrafish by administering the agents in a DMSO solution (col. 20, lines 53-58).

3) Claims 1-3,9-10,12,14-18,20-21,23,27-28,30,32-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson et al. [**PNAS**, 97:12965-12969, 2000] as evidenced by Serbedzija (US 6,656,449).

Peterson et al taught use of zebrafish as a model to screen small molecules for various phenotypic effects on the cardiovascular system (page 12965, col. 2, paragraph 3). Peterson et al taught placing embryos in 96 well arrayed plate and adding small molecules from the DiverSet E library (page 1296, col. 2, paragraph 2). Peterson et al. taught administering the agent in a DMSO solution (p. 12965, col. 2, paragraph 2), which permeabilizes the zebrafish (see Serbedzija, US 6,656,449 at col. 20, lines 53-58).

Parameters of heart function were observed as Peterson et al. teach that 32P6 causes two edematous pericardial sacs to form, mimicking cardia bifida (page 12966, col. 1, paragraph 2). 31J6 affected heart contractility (page 12968). 31J6 causes an increase in the ratio of atrium to ventricle contractions. Peterson remarks that this particular small molecule causes effects correlating to second-degree atrioventricular heart block observed in humans, which is correlating the effect of the agent in the zebrafish with a predicted effect on heart function in humans. Thus, Peterson et al. administered small molecules to fish. Peterson evaluated parameters of heart function including structural development and contractility.

4) Claims 1-3,5,8-9,11-12,14-21,22-24,27,30-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Artemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), hereafter referred to as '874.

'874 teaches use of zebrafish embryos and larvae (page 3, lines 25-27; page 4, line 20) to screen agents for those that affect cardiac function in zebrafish (paragraph 0050 and 0060) using a 24 well array format (p.4, line 33). Parameters to be evaluated included heart rate, rhythm, contractility (p. 4 lines 15-18), which are measured in vivo in the intact fish. '874 teaches correlating effects found in zebrafish to

effects on humans in teaching that various medications used in humans that have cardiac-related side effects has similar effect in zebrafish and thus the fish is an excellent test system for the side-effects of other potential drugs in humans (page 5, line 20-page 6, line 18). '874 teaches use of a number of small molecule drugs. '874 teaches treatment with multiple agents, including a second test agent (page 6, lines 20- page 7, line 7).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 4,36,37, 41,42,49,50 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zon (US2005/0155087; EFD 12/17/2001) as evidenced by Serbedzija (US 6,656,449) as applied to claim1-3,9-12,14-21,23,27-28,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS).

The teachings of Zon are set forth above. Zon did not teach measuring ejection fraction, contraction fraction, conduction velocity, repolarization or Q-T interval as required by claim 4 or use of an EKG (claims 37 and 50) or measurement of QT interval (claim 41). .

However, Camm taught the relevance to measuring QT interval using EKG (ECG) as a parameter of heart function as familial long QT syndrome is an inherited disease in humans.

One of skill in the art would be motivated to perform the screen taught by Zon wherein the parameter measured is QT interval because the QT interval was well known to be a parameter affected in human disease as demonstrated by Camm. One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease in humans and other mammals.

One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 4,36,37, 41,42,49,50 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serbedzija (US 6,656,449, filed 09/23/2000) as applied to claims 1-3,5,9-12,14-21,23-24,27-28,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS).

The teachings of '449 are set forth above. '449 did not teach measuring ejection fraction, contraction fraction, conduction velocity, repolarization or Q-T interval as required by claim 4 or use of an EKG (claims 37 and 50) or measurement of QT interval (claim 41). .

However, Camm taught the relevance to measuring QT interval using EKG (ECG) as a parameter of heart function as familial long QT syndrome is an inherited disease in humans.

One of skill in the art would be motivated to perform the screen taught by '449 wherein the parameter measured is QT interval because the QT interval was well known to be a parameter affected in human disease as demonstrated by Camm. One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease in humans and other mammals.

One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

3) Claims 4,36,37, 41,42,49,50 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. [PNAS, 97:12965-12969, 2000] as evidenced by Serbedzija (US 6,656,449) as applied to claims 1-3,9-10,12,14-18,20-21,23,27-28,30,32-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS).

The teachings of Peterson are set forth above. Peterson did not teach measuring ejection fraction, contraction fraction, conduction velocity, repolarization or Q-T interval as required by claim 4 or use of an EKG (claims 37 and 50) or measurement of QT interval (claim 41). .

However, Camm taught the relevance to measuring QT interval using EKG (ECG) as a parameter of heart function as familial long QT syndrome is an inherited disease in humans.

One of skill in the art would be motivated to perform the screen taught by Peterson wherein the parameter measured is QT interval because the QT interval was well known to be a parameter affected in human disease as demonstrated by Camm. One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease in humans and other mammals.

One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

4) Claims 4,36,37, 41,42,49,50 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Artemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), hereafter referred to as '874 as evidenced by Serbedzija (US 6,656,449) as applied to claims 1-3,5,8-9,11-12,14-21,22-24,27,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS).

The teachings of '874 are set forth above. '874 did not teach measuring ejection fraction, contraction fraction, conduction velocity, repolarization or Q-T interval as required by claim 4 or use of an EKG (claims 37 and 50) or measurement of QT interval (claim 41). .

However, Camm taught the relevance to measuring QT interval using EKG (ECG) as a parameter of heart function as familial long QT syndrome is an inherited disease in humans.

One of skill in the art would be motivated to perform the screen taught by '874 wherein the parameter measured is QT interval because the QT interval was well known to be a parameter affected in human disease as demonstrated by Camm. One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease in humans and other mammals.

One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1,11,12,17-19,40 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1,2,9,10 and 15-17 and 19 of copending Application No. 11/149,662. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Primary Examiner
Art Unit 1632